PharmX, Inc.

November 30, 1999

Dr. Lonnie Luther
Quality Assurance Support Team (HFV-102) Room 387
FDA Center for Veterinary Medicine
750 Standish Place
Rockville, MD 20855

Dear Dr. Luther:

Enclosed please find a suitability petition submitted on behalf of PharmX, Inc. of Portland, ME. PharmX requests a consideration of this suitability petition to file an ANADA for PalaBute™ (phenylbutazone) Pellets for horses.

Please call if you have questions.

Sincerely,

Hugh H. Johnston, M.D.
CEO and Medical Director

Enc.

75 Market Street
Suite 305
Portland, Maine 04101
tel: (207) 772-2129
fax: (207) 773-5975
e-mail: PharmX@Phrmx.com

99P-5331

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PharmX, inc.

SUITABILITY PETITION

Identification of Petitioner:
This suitability petition is submitted on behalf of PharmX, Inc., 75 Market St, Suite 305, Portland, Maine 04101 under section 5 12(n)(3) of the Federal Food, Drug, and Cosmetic Act.

Action Requested:
The petitioner requests permission from the Commissioner to file an Abbreviated New Animal Drug Application (ANADA) for a different dosage form of an approved pioneer product. The pioneer product is Phoenix Scientific Inc.'s PhenylBute™ (phenylbutazone tablets, USP) approved by the Food and Drug Administration under NADA 91-818. A copy of the pioneer product labeling is provided (Attachment 1).

The ANADA will provide for the use of a palatable dosage form for administration in the grain ration for horses (or dissolved in water and administered orally via syringe) rather than the tablet form of the pioneer product. Both the proposed and the pioneer products are delivered orally. The active ingredient (phenylbutazone) will be delivered in a palatable pelletized base formulated to contain 1 gram of phenylbutazone per pouch of pellets. The pioneer product is formulated to contain 1 gram of phenylbutazone per tablet. Both the proposed and pioneer products are provided to affected animals at the rate of 2-4 mg phenylbutazone per pound of body weight.

The product labeling will provide for indications, recommended dosages, contraindications, precautions and warnings identical to the pioneer product. Draft labeling for the proposed product is provided (Attachment II).

The proposed product label differs from the pioneer product specifically as follows:

1. Labeled as "Pellet" rather than "Tablet".
2. Contents are labeled per pouch of pellets (phenylbutazone in g/pouch) rather than per tablet.
3. The Dosage and Administration instructions are revised to describe delivery of the pelleted drug product mix in the grain ration and dissolution of the product in water with administration orally via syringe if necessary.
4. It is anticipated that stability studies will support storage at room temperature conditions.

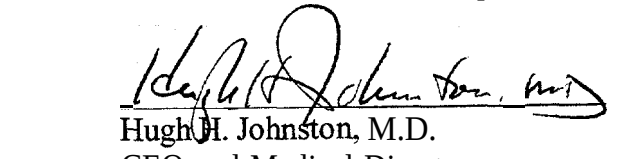
75 Market Street
Suite 305
Portland, Maine 04101
tel: (207) 772-2129
fax: (207) 773-5975
e-mail: PharmX@ Phrmx.com

Statement of Grounds:
The proposed product contains the same active ingredient and will be labeled with the same indications, recommended dose rates, contraindications, precautions and warnings as the approved pioneer product. Because of oral administration and absorption after the phenylbutazone is dissolved in the stomach, the clinical effect for both drugs is expected to be similar. The sponsor intends to provide results of blood level bioequivalency testing to demonstrate efficacy and safety of the product, palatability information for the product, and information to demonstrate the pellets dissolve adequately in water.

Environmental Impact:
The action of submitting this Suitability Petition and its review by the FDA-Center for Veterinary Medicine is not expected to have an environmental impact. The action requested qualifies for categorical exclusion under 21 CFR $25.30 (h) from the requirement for an environmental assessment.

Economic Impact:
The Commissioner will provide an "Economic Impact" analysis of this action upon request.

Certification:
PharmX, Inc. certifies that this suitability petition contains all information known to them which is unfavorable to the petition.



9/11/30
Date

Hugh H. Johnston, M.D.
CEO and Medical Director
PharmX, Inc.
75 Market St., Suite 305
Portland, Maine 04 10 1

Attachments:

1. Pioneer Product Label
2. Proposed Product (PalaBute™) Label

ATTACHMENT 1

PP

PHENYLBUTE''' TABLETS

(Phenylbutazone Tablets, USP) 1 gram

NADA 91-818, Approved by FDA

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Phenylbutazone chemically is 4-butyl-1, 2 diphenyl-3, 5-pyrazolidinedione.

$C_{19}H_{20}N_2O_2$

Mol. wt. 308.36

Each tablet contains 1 g of phenylbutazone

BACKGROUND PHARMACOLOGY: Phenylbutazone was first synthesized in 1948 and introduced into human medicine in 1949. Kuzell (1), (2), (3), Payne, (4), Fleming, (5) and Denko, (6) demonstrated the clinical effectiveness of phenylbutazone in gout, gouty arthritis, acute arthritis, acuto rhoumatism and various other rheumatoid disordors in humans. Fabre (7), Domenjoz, (8), Wilhelmi, (9) and Yourish, (10), hevo established the anti-rheumatic and anti-inflammatory activity of phenylbutazone. It is entirely unrelated to the steroid hormones.

Toxicity of phenylbutazone has been investigated in rats and mice (11), and dogs (12).

Phenylbutazone has been used by Camberos (13). In thoroughbred horses. Favorable results were reported in cases of traumatism, muscle rupture, strains and inflammations of the third phalanx. Results were not as favorable in the periodic treatment of osteo-arthritis of the stifle and hip, arthrosis of the trapezious muscles end general arthritis. Suitor, (14) reported a favorable response in chronic equine arthritis of long duration, fair results In severely bruised mare and poor results in two cases where the condition was limited to the third phalanx.

INDICATIONS: Phenylbutezone is for the relief of inflammatory conditions associated with the musculoskeletal system in horses.

DOSAGE AND ADMINISTRATION: For Horses Only: Orally 1 to 2 tablets per 500 pounds of body weight, but not to exceed 4 g per animal dally. Use high dose for the first 48 hours, then gradually reduce to a maintenance dose.

CONTRAINDICATIONS: Use with caution In patients who hsve history of drug allergy.

PRECAUTION: In the treatment of inflammatory conditions associated with infections, specific anti-infective therapy should be used concurrently.

WARNING: Not for horses intended for food.

HOW SUPPLIED: Tablets containing 1 gram of phenylbutazone are supplied in bottles of 100 tablets.

Store at controlled room temperature, 20' to 25'C (68' to 77'F)

References:

1. Kuzell, WC, Schaffarzick, RW, Naughler, WE, Gandle, C and Mankle, EA: A.M.A. Arch. Inst. Med., 92,648 (1953).
2. Kuzell, WC, Schafferzick, RW, Brown, B and Mankle, EA: J.A.M.A. 149; 729 (1952).
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7. Fabre, J, et at: Semain. Hop. (Paris) 31; 87 (1955).
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9. Wilhelmi, G end Pulver, R: Arzneimittel-Forsch, 5; 221 (1965).
10. Yourish, W, Paton, B, Brodie, B, Burns, J: A.M.A. Arch. Ophth., 53: 264 (1965).
11. Hazelton, LW, Tusing, TW and Hollana, EG: J. Pharmacol, Exper. Ther., 109; 387 (1953).
12. Ogilvie, FB and Sutter, MD: Vet, Med 52; 492-4 (1957).
13. Camberos, HR: Rev. Med. Vet. (Buenos Arles) 38: 9 (1956).
14. Sutter, MD: Vet. Med., 53; 83 (Feb. 1958).
15. Gabriel, KL, Martin, JE: J. Am. Vet. Med. A. 140; 334-41 (Feb. 1962).

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Manufactured By:
Phoenix Scientific. Inc.
St. Joseph, MO 64503

Manufactured For.
Phoenix Pharmaceutical, Inc.
St. Joseph, MO 64506

ATTACHMENT 2

PalaBute™

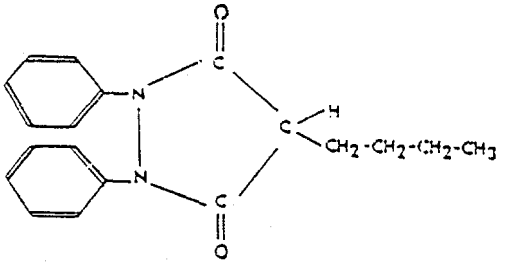
Brand of Phenylbutazone

Caution:

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description

Phenylbutazone is the accepted generic name of the drug known chemically as 4-butyl- I, 2-diphenyl-3, 5-pyrazolidinedione. It has the following chemical structure.



Mol. wt 308.38 $C_{19}H_{20}N_2O_2$

Fhenylbutazone is a white crystalline solid, slightly soluble in water, and soluble in some organic solvents. It has no odor and a slightly bitter taste.

Background Pharmacology

Phenylbutazone is a non-hormonal anti-inflammatory agent. It is unrelated to the corticosteroid anti-inflammatory agents. The anti-inflammatory activity of phenylbutazone has been shown in lower animals (1) and in man (2). The greatest amount of data on efficacy is in man (3-6). Studies in horses have reported useful anti-inflammatory activity (7-10). Metabolic studies in horses have shown that the drug is well absorbed when administered orally with a balling gun. The apparent half-life is 3.5 hours (11,12).

The effectiveness of phenylbutazone in man for acute rheumatism, gout, gouty arthritis and other rheumatoid disorders has been demonstrated by several clinicians. including Kuzell (2), Payne (3), Fleming (4) and Denko (5). Clinical trials by many investigators. including Yourish (6), Fabre (13), Domenjoz (14) and Wilhelmi (15) have established the anti-rheumatic and anti-inflammatory activity of phenylbutazone.

Phenylbutazone was reported effective in the treatment of painful musculoskeletal conditions in dogs, including posterior paralysis associated with intervertebral disc syndrome, fractures. arthritis and injuries to limbs and joints (11). The efficacious use of phenylbutazone in two arthritic dogs was described by Letter (16). Treatment was long term and no signs of toxicity were reported. Ogilvie and Sutter (17) found phenylburazone to provide rapid relief in 19 cases of canine inflammatory conditions. mainly of posterior paralysis but also including posterior weakness. rheumatism and other conditions associated with lameness and musculoskeletal weakness.

Sutter (8) found phenylbutazone treatment gave a favorable response in chronic equine arthritis. Davidson and Franks (10) found phenylbutazone to be effective in the treatment of lameness in horses due to post-operative inflammation following joint surgery. Phenylbutazone reduced the severity and duration of pain, as well as the number of horses showing pain. Camberos (7) successfully treated thoroughbred horses with arthritis and chronic arthritis (e.g osteoarthritis of medial and distal bones of the hock, arthritis of the stifle and hip, arthritis of the spine, chronic hip pain, chronic pain in the trapezius muscles and generalized arthritis). A less favorable response was noted in cases of traumatic muscle rupture, strains and inflammations of the third phalanx.

Indications:
Phenylbutazone is used for the relief of inflammatory conditions associated with the musculoskeletal system in horses.

Contraindications:
Use with caution in horses with a history of drug allergy.

Precautions:
In the treatment of inflammatory conditions of horses associated with infections, specific anti-infective therapy is required.

Warning:
Not for use in horses intended for food.

Side Effects:
Doses of phenylbutazone higher than recommended have been shown to produce intestinal ulcerative lesions (12). Necrotizing phlebitis in the portal vein has been observed in horses receiving higher doses for extended periods of time (13).

Dosage and Administration
The oral dose for horses is 2 to 4 PalaBute™ pouches or 2 to 4 grams phenylbutazone per 1000 lbs. per day mixed in the grain ration. The total daily dose should be limited to 4 grams per day. Because of the relatively short half-life of the drug, administration every eight hours is the most satisfactory schedule. Because PalaBute is a palatable medication, there should be no refusal of medicated feed. However, should the horse refuse to accept them the pellets may be dissolved in water and given orally via syringe.

Response to phenylbutazone is usually prompt. If there is no significant clinical effect in 5 days, a reevaluation of the diagnosis and treatment should be made.

How Supplied:
PalaBute™ is supplied in dose-unit pouches containing 1-gram phenylbutazone in cartons of 20 packers.

References

1. Lieberman L.L. *Jour. Amer. Vet. Med. Assoc.* 125:128, 1954.
2. Kuzell, W.C., Schaffarzick, R.W., Naugler, W.E., Gaudii G. and Mankle, E.A. *A.M.A. Arch. Int. Med.* 92:646, 1953.
3. Payne, R.W., Shetlar, MR., Farr, C.H., Hellbaum, A.A. and Ishmael, W.K. *J.Lab. Clin. Med.* 45:331, 1995.
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10. Davidson, A.H. and Franks, W.C. *Mod. Vet. Practice.* 47:46, *1966.*
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Manufactured for PharmX, Inc., Portland, ME 04101